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ITJ

ISSN 1812-5638

INFORMATION TECHNOLOGY JOURNAL

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Information Technology Journal 11 (1): 20-29, 2012
ISSN 1812-5638 / DOI: 10.3923/itj.2012.20.29

Fuzzy Inference Mechanism Based Automatic Elastic Registration of Two-dimensional Gel Electrophoresis Images

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Abstract: A key technique for protein analysis is the geometric alignment of two-dimensional polyacrylamide gel electrophoresis (2-D PAGE), i.e., 2-D PAGE image registration. In this study, the adaptability in elastic image registration was emphasized. According to the characteristics of 2-D gel image registration, a fuzzy-inference-rule based flexible model (FIM-FM) is proposed to model the complex transformation between 2-D gel image pairs. By introducing the concept of motion estimation, the parameter learning rules of the proposed model are derived for registration. The experiments show that the proposed algorithm is highly effective for registration of 2-D gel images and is competitive to the existing state-of-the-art algorithms.

Key words: Fuzzy inference mechanism, automatic elastic registration, two-dimensional gel electrophoresis images, image registration, adaptive learning, image matching

INTRODUCTION

Two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) is one of the core techniques for separating complex protein mixtures in the majority of proteome projects (Klose, 1975; O'Farrell, 1975; Dowsey *et al*., 2003; Subair *et al*., 2005; Abdalla and Deris, 2005). By this technique a very large number of proteins can relatively easily and simultaneously be separated, identified and characterized. This is important for understanding protein function and thus enables the development of new and more effective drugs. In many proteomic projects, it is necessary to determine spatial correspondence between spots on sets of 2-D gel images such that all points of one image physically correspond to the points in another image. In order to realize this aim, the key task here is to find an optimal geometric transformation between image data which is known as the image registration problem. Image registration has been extensively studied and a large number of image registration algorithms have been proposed. These algorithms contain rigid and elastic algorithms for several practical applications, such as medical diagnosis, machine vision and so on (Ratha and Bolle, 1998; Jain *et al*., 1997; Fang and Tang, 2006; Stone *et al*., 2001). The complete review of image registration is beyond the scope of this study and the surveys about image registration can see by Maurer and Fitzpatrick (1993), Brown (1992), Van den Elsen *et al*. (1993), Maintz and Viergever (1998), Lester and Arridge (1999) and Periaswamy (2003). Here, this study only focus on the existing algorithms designed for 2-D gels image registration. Previous work on 2-D gel image registration can be roughly classified into landmark based-algorithms (Appel *et al*., 1997; Lemkin, 1997; Efrat *et al*., 2002; Potra and Liu, 2006; Rogers and Graham, 2007), intensity-based algorithms (Baker *et al*., 2000; Smilansky, 2001; Veeser *et al*., 2001) and landmark-and-intensity-based algorithms (Rohr *et al*., 2004; Sorzano *et al*., 2005). Landmark-based algorithms and intensity-based algorithms are the main categories. The landmark-based algorithms are more computational efficiency and robust to intensity differences. However, these algorithms usually need user-interaction. The intensity-based algorithms can directly exploit the image intensities and use more image information. Except for these two principal classes of registration algorithms for 2-D algorithms based on both landmark gels images, some researchers fused these two strategies and presented the 2-D gel image registration and intensity which can be seen in Rohr *et al*. (2004) and Sorzano *et al*. (2005). This kind of algorithms can have the merits of the above two category methods. However, in order to balance the influence of

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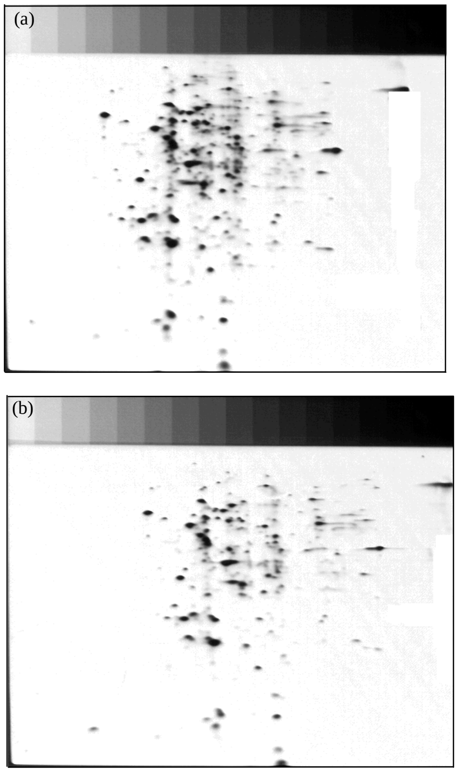

Fig. 1(a-b): A 2-D gel image pair with complex geometric and intensity transformations

two strategies this kind of algorithms often need to adjust much more parameters (Sorzano *et al*., 2005).

In recent years, the intensity based automatic registration algorithms for 2-D gel images attract more attention of researches for their easy use. In this study, the focus is the intensity-based automatic registration of 2-D gel images (Baker *et al*., 2000; Smilansky, 2001; Veeser *et al*., 2001).

Due to complex physical and chemical processes, the locations and intensities of proteins generally vary in different images (Fig. 1) and therefore, adaptive registration algorithms have to be applied. Although, some registration algorithms have been presented to implement the registration of 2-D gel images (Ravichandran and Ravindran, 2007), there still exist many issues to be addressed before 2-D gel image registration can be effectively and widely applied. In this study, we focus on two relatively important issues in the intensity based automatic 2-D gel image registration: (1) how to effectively model the complex geometric transformation and the intensity variation between the 2-D gel images to be registered and (2) how to adaptively learn precise model parameters of the adopted model to realize the automatic registration of 2-D gel images. In order to cope with these two difficulties, the adaptability in image registration should be emphasized. Based on the fuzzy inference mechanism, a highly adaptive Fuzzy-inference-rule based flexible model (FIR-FM) is proposed to model the complex geometric and intensity transformations. In addition, by introducing the concept of motion estimation and the corresponding Sum-of-squared-difference (SDD) objective function, the parameter learning rules for the proposed FIR-FM model are derived and presented. With the proposed FIR-FM model and the associated parameter learning rules, an automatic elastic image registration algorithm can be obtained for 2-D gel image registration. The proposed FIR-FM-based algorithm can obtain the complex nonlinear transformations and learn the model parameters effectively through parameter learning rules. As the proposed method is based on fuzzy inference mechanism, it keeps many of the advantages of fuzzy inference systems, e.g., it can adaptively utilize the domain knowledge to improve the modeling performance.

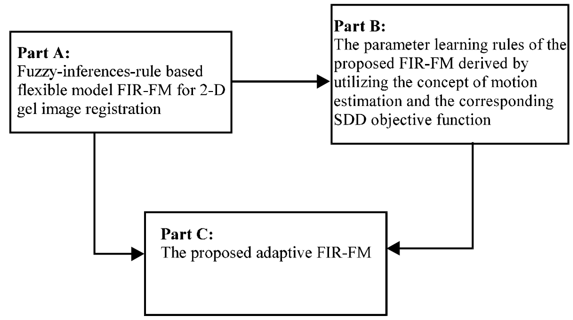

Fig. 2: The proposed general framework for 2-D gel image registration

Proposed general framework for 2-d gel image registration: The proposed general framework for 2-D gel image registration in this study is as shown Fig. 2. The proposed framework is composed of three major parts. Part A is the proposed fuzzy-inference-rule based flexible model (FIR-FM) which can approximate the complex geometric and intensity transformations in elastic registration of 2-D gel image pair. Part B contains the adaptive learning rules of the proposed model derived by utilizing the concept of motion estimation and the corresponding SDD objective function. Part c presents an adaptive FIR-FM based automatic elastic image registration algorithm for 2-D gel images. In the flowing sections, we will give the descriptions of these three parts in detail.

A FUZZY-INFERENCE-RULE BASED FLEXIBLE MODEL (FIR-FM) FOR 2-D GEL IMAGE REGISTRATION

Geometric and intensity transformation in gel image registration: Here, the geometric and intensity transformations in image registration are described. Here, I_r and I_s are used to denote the reference image and the source image, respectively. A reference image I_r can be seen as a set of pixels in the image, i.e.:

$$I_r = p_{r,l},\ l = 1, 2, ..., N \tag{1}$$

where, $p_{r,l}$ is the l-th pixel in I_r. Each pixel can be characterized by location vector $p_{r,l} = (p_{r,l1}, p_{r,l2})^T = (x_l, y_l)^T$ and intensity value $Z_{r,l}$, where (x_l, y_l) denotes the spatial coordinate of $p_{r,l}$ in I_r.

Suppose the pixel $p_{r,l}$ in the reference image I_r corresponds to the pixel $p_{r,l}$ in the source image I_r. With the location vector and the intensity value of $p_{s,l}$ denoted as $p_{s,l} = (p_{s,l1}, p_{s,l2})^T = (x_l', y_l')^T$ and $Z_{s,l}$, respectively, the relationships between the two corresponding pixels can be formulated as:

$$x_l' = g_x(x_l, y_l),\ y_l' = g_y(x_l, y_l) \tag{2}$$

$$z_{s,l} = f_z(z_{r,l}) \tag{3}$$

where, g (.) and f_z (.) are the geometric and intensity transformation functions, respectively. A commonly used geometric transformation function in image registration is affine linear transformation which can be formulated as:

$$x_l' = m_1 x_l + m_2 y_l + m_3,\ y_l' = m_4 x_l + m_5 y_l + m_6 \tag{4}$$

where, the transformation parameters can be written as a vector $m = (m_1\ m_2\ m_3\ m_4\ m_5\ m_6)^T$. For the intensity transformation function f_z (.), the linear transformation in (5) is often adopted for image registration (Periaswamy, 2003; Hager and Belhumeur, 1998; Periaswamy and Farid, 2003, 2006):

$$z_{s,l} = c_l . z_{r,l} + b_l \tag{5}$$

where c_l and b_l denote the linear transformation parameters of the corresponding intensity value.

In almost all of the rigid image registration algorithms, it is assumed that the transformations between all the corresponding pixels in two images conform to the same transformation function. It is appropriate for the situations where only the same transformation exists between two images to be registered. However, the assumption can not be true in registration of 2-D gel images. The real transformations between two gel images are actually so complex that a highly nonlinear geometric transformation is typically required. Therefore, how to effectively model such a complex transformation is a critical task to realize effective registration of 2-D gel images. In this study, attempt has been made to address this issue by incorporating the strong modeling capability of fuzzy inference systems into elastic image registration of 2-D gel images.

Fuzzy-inference-rule based flexible model: Fuzzy inference mechanism is one of the most important intelligent modeling techniques (Dianyou *et al*., 2007; Yufeng *et al*., 2011; Radha and Rajagopalan, 2007). It has been extensively applied to systems modeling, intelligent control, system identification and so on. The design of fuzzy inference rules is the core of a fuzzy inference system. With the fuzzy inference rules, a fuzzy inference system can realize a highly nonlinear approximation. Unlike other modeling methods like neural networks which are often taken as black boxes and thus are unacceptable in many real applications, fuzzy-inference-rule based modeling methods offer a much better interpretation. Another advantage of fuzzy-inference-rule based modeling methods is that the domain knowledge can be easily incorporated by the fuzzy inference rules to enhance the modeling capability. This subsection describes how the fuzzy inference rules can be used to realize the complex geometric and feature transformation in elastic 2-D gel image registration.

With the location and/or intensity information of all the pixels, an image can be partitioned into several fuzzy regions (using a clustering technique or other partitioning techniques). As exemplified in Fig. 3, a fuzzy region is represented by a fuzzy set. For a fuzzy set A^i, one may construct the following fuzzy inference rule for elastic image transformation of 2-D gel image pair.

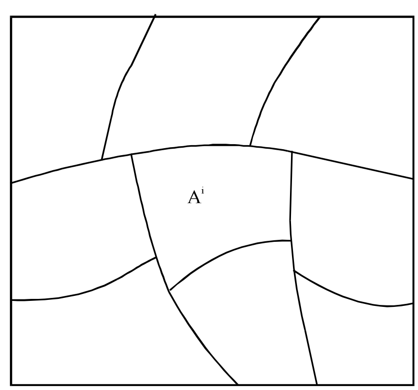

Fig. 3: Fuzzy partition of an image

$$\text{Rule i: IF } p_1(x,y) \text{ is } A^i\text{, THEN } m_1^i = m^i \text{ and } c_1^i = c^i \text{ and } b_1^i = b^i \quad (6)$$

for i = 1,..., R, where m^i denotes the affine linear transformation parameter in (4) associated with the fuzzy set A^i, c^i and b^i are the corresponding intensity transformation parameters associated with the fuzzy set A^i which are introduced in Eq. 5.

For the given fuzzy inference rule in (6), the IF-part denotes the inference conditions and the THEN-part denotes the corresponding inference results. If we take the location vector of pixel p_l as the input of the inference rule and a vector $u_i = (u_{i1}, u_{i2})^T$ as the center of fuzzy set A^i, the rule in (6) may be further expressed as:

$$\begin{aligned}&\text{Rule i: IF } x_1 \text{ is } A_1^i \text{ and } y_1 \text{ is } A_2^i\text{, THEN } m_1^i = m^i \\ &\text{and } c_1^i = c^i \text{ and } b_1^i = b^i\end{aligned} \quad (7)$$

where, A_j^i denotes the fuzzy subset of A^i for the j-th dimensional feature of the input vector. The outputs of a fuzzy inference system are often obtained by the weighted sum of all rules. For our fuzzy inference system designed for elastic 2-D image registration, the final output variables, $m = (m_{l1}\ m_{l2}\ m_{l3}\ m_{l4}\ m_{l5}\ m_{l6})^T$, c_l and b_l can be expressed as:

$$m_1 = \frac{\sum_{i=1}^{R} w_1^i m_1^i}{\sum_{i=1}^{R} w_1^i} = \frac{\sum_{i=1}^{R} w_1^i m^i}{\sum_{i=1}^{R} w_1^i} = \sum_{i=1}^{R} w_1^{\wedge i} m^i \quad (8)$$

$$c_1 = \frac{\sum_{i=1}^{R} w_1^i c_1^i}{\sum_{i=1}^{R} w_1^i} = \frac{\sum_{i=1}^{R} w_1^i c^i}{\sum_{i=1}^{R} w_1^i} = \sum_{i=1}^{R} w_1^{\wedge i} c^i \quad (9)$$

$$b_1 = \frac{\sum_{i=1}^{R} w_1^i b_1^i}{\sum_{i=1}^{R} w_1^i} = \frac{\sum_{i=1}^{R} w_1^i b^i}{\sum_{i=1}^{R} w_1^i} = \sum_{i=1}^{R} w_1^{\wedge i} b^i \quad (10)$$

In Eq. 8-10, w_1^i denotes the weight of the i-th rule for the *l*-th input variable and:

$$w_1^{\wedge i} = w_1^i \Big/ \sum_{k=1}^{R} w_1^k$$

is the corresponding normalized weight. Here, w_1^i can be obtained by computing the fuzzy memberships of different features of the input vector using the operation of certain T-norm. If Gaussian membership function and multiplication T-norm are taken, w_1^i can be formulated as:

$$w_1^i = \prod_{j=1}^{n} \exp\left(\frac{\| p_{lj} - u_{ij} \|^2}{\sigma_{ij}^2}\right) \quad i = 1, 2, ..., R \quad (11)$$

where, σ_{ij} (j = 1, 2,..., n) is the spread of the corresponding Gaussian membership function; n is the dimensional number of the input variable. Here, u_{ij} and σ_{ij} can be estimated using clustering techniques (Bezdek, 1982; Bezdek *et al*., 1999; Keller *et al*., 1985; Krishnapuram and Keller, 1993; Wei *et al*., 2009; Dechang and Xiaolin, 2008). In other words, the obtained cluster centers of the input dataset can be taken as the centers of the corresponding fuzzy membership functions and σ_{ij} can be estimated as the standard deviations of the corresponding clusters in the input dataset. For the rule in (7), the weight of the i-th rule in (11) can be further formulated as:

$$w_1^i = \exp\left(\frac{(x_1 - u_{i1})^2}{2\sigma_{i1}^2}\right) \cdot \exp\left(\frac{(y_1 - u_{i2})^2}{2\sigma_{i2}^2}\right) \quad (12)$$

In fact Eq. 8-10 formulate a Fuzzy-inference-rule based Flexible Model (FIR-FM) for the nonlinear transformation in elastic image registration. Obviously, the proposed model naturally inherits the strong approximation capability of fuzzy inference systems. In the following section, the parameter learning rules for the proposed FIR-FM are derived. With the obtained model parameters by adaptive learning, the precise transformation between the gel image pair can be obtained accordingly.

Parameter learning: In this subsection, we derive the parameter learning rules of the proposed model FIR-FM and present a FIR-FM based automatic elastic image registration algorithm. The parameter learning rules of FIR-FM are firstly derived for image registration and based on which an elastic registration algorithm is proposed for 2-D gel image registration.

In Memin and Perez (1998) and Hellier *et al*. (2001, 2000) considered the motion estimation (Liao and Chu, 2009) for parameter estimation of a transformation model in image registration. Here, a similar way is adopted for the parameter learning rules of the proposed FIR-FM model.

Let us take the reference image I_r as the template image at time I_0 and denoted as I_{t0} and take the source image I_s as the deformed image of the template image I_r at time t_1 and denoted as I_{t1}. Now, the parameter estimation of a transformation model in image registration becomes a motion estimation problem. By introducing the temporal variable t, the intensities of two images can be expressed as the following functions of space and time variables in a unified form:

$$\begin{aligned} z_{r,l} &= f_r(x_l, y_l) = f\ (x_l, y_l, t_0) \\ z_{s,l} &= f_s(x_l', y_l') = f\ (x_l', y_l', t_l) \end{aligned} \tag{13}$$

for l = 1, 2,..., N. In order to estimate the motion parameters, an error metric function is usually adopted, e.g., the commonly used sum-of-squared differences (SSD) objective function (Hager *et al*., 2004; Farid and Simoncelli, 2004). In our study, this objective function is adopted as:

$$J_{obj} = E_{SSD}(z_{r,l}', z_{s,l}) = \sum_{l=1}^{N} | z_{r,l}' - z_{s,l} |^2 \tag{14}$$

$$z_{r,l}' = c_l \cdot z_{r,l} + b_l \tag{15}$$

Substituting Eq. 15 into Eq. 14, we have:

$$J_{obj} = \sum_{l=1}^{N} \left(c_l \cdot z_{r,l} + b_l - z_{s,l} \right)^2 \tag{16}$$

Furthermore, by substituting Eq. 13 into Eq. 16, we have:

$$J_{obj} = \sum_{l=1}^{N} \left(c_l \cdot f\ (x_l, y_l, t_0) + b_l - f\ (x_l', y_l', t_l) \right)^2 \tag{17}$$

Using the first-order truncated Taylor series expansion, $f(x_l', y_l', t_l)$ can be approximately expressed as:

$$\begin{aligned} f(x_l', y_l', t_l) &= f(m_{l1}x_l + m_{l2}y_l + m_{l3}, m_{l4}x_l + m_{l5}y_l + m_{l6}, t_l) \\ &\approx f(x_l, y_l, t_0) + (m_{l1}x_l + m_{l2}y_l + m_{l3} - x_l) \cdot f_x(x_l, y_l, t_0) \\ &\quad + (m_{l4}x_l + m_{l5}y_l + m_{l6} - y_l) \cdot f_y(x_l, y_l, t_0) \\ &\quad + (t_l - t_0) \cdot f_t(x_l, y_l, t_0) \end{aligned} \tag{18}$$

where $f_x(.)$, $f_y(.)$ and $f_t(.)$ are the corresponding spatial and temporal derivatives of f (.). By normalizing t_l-t_0 = 1 and omitting the variable notations in the functions f (.), f_x (.), f_y (.) and f_t (.) and substituting Eq. 18 into 17, the SSD objective function in Eq. 17 can be approximately formulated as:

$$J_{obj} = E' \tag{19}$$

Where:

$$\begin{aligned} E' &= \sum_{l=1}^{N} \Big\{ \left[c_l f + b_l \right] - \left[f + (m_{l1}x_l + m_{l2}y_l + m_{l3} - x_l) \cdot f_x \right. \\ &\quad \left. + (m_{l4}x_l + m_{l5}y_l + m_{l6} - y_l) \cdot f_y + f_t \right] \Big\}^2 \\ &= \sum_{l=1}^{N} \Big[-(x_l f_x) \cdot m_{l1} - (y_l f_x) \cdot m_{l2} - f_x \cdot m_{l3} - (x_l f_y) \cdot m_{l4} \\ &\quad - (y_l f_y) \cdot m_{l5} - f_y \cdot m_{l6} + c_l f\ + b_l \\ &\quad + (x_l f_x + y_l f_y - f\ - f_t) \Big]^2 \end{aligned} \tag{20}$$

Let a_l = $(c_l\ b_l)^T$, v_l = $(x_l\, f_x\ \ y_l\, f_x\ \ f_x\ \ x_l\, f_y\ \ y_l\, f_y\ \ f_y)$, q_l = $(\text{-}f\ \ \text{-}1)^T$ and h_l = $x_l\, f_x$+$y_l\, f_y$-f-f_t. Eq. 20 can be rewritten as:

$$E' = E'(m_l, a_l) = \sum_{l=1}^{N} \left(h_l - v_l^T m_l - q_l^T a_l \right)^2 \tag{21}$$

Then, by substituting Eq. 8-10 into 21, we have:

$$E' = E'(m^i, a_k^i) = \sum_{l=1}^{N} \left(h_l - v_l^T \sum_{i=1}^{R} w_l'^i m^i - q_l^T \sum_{i=1}^{R} w_l^i a^i \right)^2 \tag{22}$$

where, a^i = $(c^i\ b^i)^T$.

Now, the SSD objective function becomes the function of the model parameters of the proposed FIR-FM, i.e.:

$$J_{obj} = E_{SSD}\ (z_{r,l}', z_{s,l}) = E'(m^i, a^i) \tag{23}$$

In order to obtain the precise parameters of the proposed FIR-FM for image registration, we need to minimize J_{obj}. According to the following theorem, we can easily obtain the iterative parameter learning rules for optimizing the model parameters of FIR-FM.

- **Theorem 1:** The necessary conditions of minimizing the objective function in Eq. 23 are:

$$m^i = H_{ii}^{-1} h_i - \sum_{\substack{s=1 \\ s \neq i}}^{R} H_{ii}^{-1} H_{is} m^s \tag{24}$$

And:

$$a^i = K_{ii}^{-1} k_i - \sum_{\substack{s=1 \\ s \neq i}}^{R} K_{ii}^{-1} K_{is} a^s \tag{25}$$

Where:

$$H_{ij} = \sum_{l=1}^{N} \left[(w_l'^i w_l'^j)^2\, v_l v_l^T \right] \tag{26}$$

$$h_i = \sum_{l=1}^{N} \left[(w_l'^i v_l) \left(h_l - q_l^T \sum_{s=1}^{R} w_l'^s a^s \right) \right] \tag{27}$$

$$K_{ij} = \sum_{l=1}^{N} \left[(w_l'^i w_l'^j)^2\, q_l q_l^T \right] \tag{28}$$

And:

$$k_i = \sum_{l=1}^{N} \left[(w_l'^i v_l) \left(h_l - v_l^T \sum_{s=1}^{R} w_l'^s m^s \right) \right] \tag{29}$$

Here, H^{-1} and K^{-1} are the inverse of matrices H and K, respectively.

According to theorem 1, we have the following iterative learning rules to optimize the model parameters:

$$m^i(t+1) = H_{ii}^{-1}h_i(t) - \sum_{\substack{s=1\\s\neq i}}^{R} H_{ii}^{-1}H_{is}m^s(t) \quad (30)$$

$$a^i(t+1) = K_{ii}^{-1}k_i(t) - \sum_{\substack{s=1\\s\neq i}}^{R} K_{ii}^{-1}K_{is}a^s(t) \quad (31)$$

where, t denotes the iterative number. With the above learning rules, the parameters of the proposed model FIR-FM can be obtained and accurate elastic image registration can be realized accordingly. They will be used in our FIR-FM based automatic elastic image registration algorithm to be presented by the following subsection.

A FIR-FM based automatic elastic image registration algorithm: In this subsection, we present our new elastic image registration algorithm using the parameter learning rules derived previously for FIR-FM. Let us first describe the settings of the algorithm.

- To simplify the algorithm description, two matrices T_x and T_y are introduced to record the final transformation between the corresponding pixels in two images, i.e.:

$$T_{x,l} = x_l' - x_l, T_{y,l} = y_l' - y_l \quad (32)$$

where, x_l' and y_l' are obtained using:

$$x_l' = m_{l1}x_l + m_{l2}y_l + m_{l3}, y_l' = m_{l4}x_l + m_{l5}y_l + m_{l6} \quad (33)$$

where, ml = $(m_{l1}\ m_{l2}\ m_{l3}\ m_{l4}\ m_{l5}\ m_{l6})^T$ is obtained using Eq. 8, 30 and 31. T_x and T_y can be updated in an accumulated way in the proposed registration algorithm. Here, T_x and T_y can be used to describe the final geometric transformation between the two images to be registered.

- The image registration process is realized in an iteration way. First, in order to initialize T_x and T_y the geometric transformation is estimated using the derived parameter learning rules. Then, the estimated geometric transformation is applied to the source image and a new transformation is estimated between the newly warped source image and the reference image. Thus, the matrices T_x and T_y can be accumulated with the newly estimated geometric transformation. Such a procedure is repeated until the given termination condition is satisfied

- When the parameter learning rules in Eq. 30-31 of the proposed model FIR-FM is carried out in an iteration way, the corresponding spatial/temporal derivatives need to be computed. In order to do it effectively, we adopt the method proposed in Farid and Simoncelli (2004) which is based on a set of derivative filters and is designed for multi-dimensional differentiation already exploited in Periaswamy and Farid (2003, 2006)

With these settings, our FIR-FM based automatic elastic image registration algorithm for 2-D gel electrophoresis image can be described as follows:

Algorithm: FIR-FM based automatic elastic image registration

Input: source image I_s and reference image I_r

Output: registered source image I_s'

Step 1: Set the number of fuzzy inference rules in FIR-FM; set the initial number of iterations run = 1 and take I_s as the current warped source image I_s^{run}; initialize the geometric transformation matrices T_x and T_y between I_s^{run} and I_r as zero matrices; set the termination condition, e.g., the maximum number of iterations

Step 2: Apply the parameter learning rules in Eq. 31-32 to learn the precise model parameters of the proposed model FIR-FM for the current iteration with a iterative way

Step 3: Use the obtained parameters of FIR-FM to accumulate the transformation matrices T_x and T_y; Set run = run+1 and then utilize the updated T_x and T_y to obtain the current warped source image I_s^{run}; if the termination condition is satisfied, then go to step 4; otherwise, go back to step 2

Step 4: Output the registered source image I_s', i.e., I_s^{run}

EXPERIMENTAL RESULTS

Numerical experiments were conducted for the performance test of the proposed FIR-FM based automatic elastic image registration algorithm. First, the implementation details of the proposed algorithm are described and a quantitative index is defined to evaluate the registration results. Then, the registration results of six 2-D gel image pairs are reported. For comparative study, we compare the registration results of our algorithm with the classical automatic 2-D gel image registration algorithm in Smilansky (2001).

Implementation details and evaluation index

Implementation details: In our experiments we implemented the proposed registration algorithm based on a multiscale pyramid framework with the coarse-to-fine scheme. All the images used here are gray scale one with intensity value normalized in the interval [0, 1]. For the number of fuzzy inference rules in FIR-FM, we have experimentally found that 9 to 20 are pretty good choices. Although, the adaptability of FIR-FM seems to be stronger with more rules, it is good enough for us to consider this range to achieve very satisfactory registration results.

Evaluation index: It is very difficult to quantify the quality of the registration result by a simple mathematical formula. This is usually done by an expert though visual inspection. For the quantitative comparison of the registration results, here a simple measure J_1 of the quality of registration between image I_1 and image I_2 is given as follows:

$$J_1 = \sqrt{\frac{\sum_{l=1}^{N}(|x_{1,l} - x_{2,l}|^2 + |y_{1,l} - y_{2,l}|^2)}{N}} \tag{34}$$

where, N denotes the number of the labeled landmark pairs (marked by expert) of the images I_1 and I_2; $(x_{1,l}, y_{1,l})$ and $(x_{2,l}, y_{2,l})$ are the spatial coordinates of the l-th landmark pair in the images I_1 and I_2, respectively. For the defined evaluation index J_1, the smaller the value of J_1, the better the registration effect.

Dataset and registration results

Datasets of real 2-D gel image pairs: In our experiments, six 2-D gel image pairs are collected to test the proposed registration algorithm. The six 2-D gel image pairs are describes as shown in Table 1. In the six 2-D gel image pairs, No. 1-2 are taken from the gel image dataset HEM-MALIG, No. 3-4 from the gel image dataset HL-60 and No. 5-6 from the gel image dataset FAS-serum. The gel image in gel pairs No. 1-2 is with 512×512 pixel, 8-bit, 250 microns/pixel and 22 landmarks are picked on each gel image. The gel image in gel pairs No. 3-4 is with 512×512 pixel, 8-bit, 250 microns/pixel and 21 landmarks are picked on each gel image. The gel image in gel pairs No. 5-6 is with 512×512 pixel, 8-bit, 250 microns/pixel and 52 landmarks are picked on each gel image. These gel image data are taken from a gel image database available to the public by Peter Lemkin (Lester *et al*., 1981; http://binkley.ncifcrf.gov/users/lemkin).

Registration results and analyses: In this subsection, the registration results on six gel image pairs are reported. Table 2 shows the evaluation index J_1 obtained by our algorithm (with 15 rules) and the algorithm in Smilansky (2001) on six gel image pairs. For the sake of the space of the study, only the visual registration effects of one gel pairs are presented, as shown in Fig. 4.

Table 1: The adopted six 2-D gel image pairs

No. of 2-D gel image pairs	Source image	Reference image	Come from
1	gel-HM-034	gel-HM-035	HEM-MALIG
2	gel-HM-086	gel-HM-087	HEM-MALIG
3	gel-HL60-HUM-MYEL-DIFF-008	gel-HL60-HUM-MYEL-DIFF-009	HL-60
4	gel-HL60-HUM-MYEL-DIFF-035	gel-HL60-HUM-MYEL-DIFF-036	HL-60
5	gel-FAS-CASE-M-004	gel-FAS-CASE-M-005	FAS-serum
6	gel-FAS-NA-NA-002	gel-FAS-NA-NA-003	FAS-serum

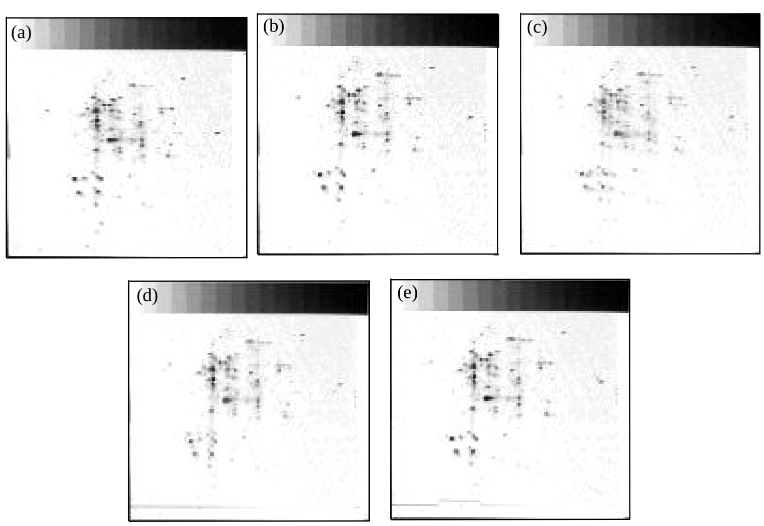

Fig. 4(a-e): The registration effects on the gel image pair 4. (a) the source gel image (b) the reference gel image (c) the superimposition of the source image and the reference image (d) the superimposition of the registered source image obtained with our algorithm and the reference image (e) the superimposition of the registered source image obtained with the algorithm in Smilansky (2001) and the reference image

Table 2: The performance comparison between our registration algorithm and the algorithm in Smilansky (2001) on six 2-D gel image

	J_1		
		(I'_s, I_r)	
Gels pairs	(I_s, I_r)	Our method (R = 15)	Method in Smilansky (2001)
1	44.6883	2.6398	6.5411
2	9.0830	1.8463	2.9934
3	18.9561	5.0770	7.4706
4	36.5725	2.6447	2.9639
5	17.4863	2.5695	3.0861
6	12.8153	3.4747	3.2136
Mean	23.2669	3.0420	4.3781

*I_s, I_r and I'_s denote the source image, reference image and registered source image, respectively

From Table 2 and Fig. 4, we can see that both the proposed algorithm and the algorithm in Smilansky (2001) can register the six gel image pairs effectively. In the six image pairs, our algorithm get the much better registration accuracies on five of the six gel image pair while on one gel image pairs, the algorithm in Smilansky (2001) get more accurate registration results.

In general, the proposed registration algorithm for 2-D gel image demonstrates a high efficacy and outperforms the algorithm in Smilansky (2001) in the registration accuracy. Therefore, the proposed algorithm is quite promising for 2-D gel image registration in the practical application.

CONCLUSIONS

In order to overcome the difficulties in 2-D gel image registration, motivated by its strength in approximation, adaptation and uncertainty handling, fuzzy inference is proposed to be incorporated by the gel image registration process. Our experimental results demonstrate the attractive performance of such an approach. In general, our work in this study can be summarized as follows. (1) A fuzzy-inference-rule based flexible model (FIR-FM) is introduced to model the complex geometric transformation and the local intensity variation. (2) The parameter learning rules of the proposed FIR-FM are derived and a FIR-FM based adaptive automatic elastic image registration algorithm for 2-D gel image is proposed. (3) The applicability of the proposed methods in different real 2-D gel images is experimentally studied.

Although, the proposed automatic elastic registration algorithm for 2-D gel images demonstrates a nicer performance, several aspects of this algorithm deserve further investigations. For example, how to further accelerate the speed of the proposed registration algorithm is very attractive to widen its applications. Moreover, when some landmarks are given, how to incorporate the known information to improve the registration performance and construct the modified registration algorithm is also a very important issue.

ACKNOWLEDGMENTS

This work was supported in part by the National Natural Science Foundation of China under Grant 60903100, Grant 60975027, in part by the Natural Science Foundation of Jiangsu Province under Grant BK2009067, in part by the Fundamental Research Funds for the Central Universities under Grant JUSRP21128, in part by the Opening Project of Jiangsu Engineering R and D Center for Information Fusion Software under Grant SR-2011-01 and in part by the Opening Project of Provincial Key Laboratory for Computer Information Processing Technology, soochow university.

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